Allergy Abstracts

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Use of Diphtheria Toxin and Toxoid in the Study of Immediate and Delayed Hypersensitivity in Man. Pappenheimer, A. M., Jr.: J. Immunol. **75**: 259, 1955. (Presidential Address, American Association of Immunologists, April 12, 1955.)

A system suitable for the study of hypersensitive mechanisms in man should possess the following properties: (a) sensitization to the antigen should not be inconvenient or dangerous to the host; (b) the antigen should be available in a purified state and should be well characterized; (c) quantitative estimation of both antigen and antibody should be feasible. The diphtheria toxin-antitoxin reaction meets these specifications.

The common forms of hypersensitive reactions have all been observed in sensitive human beings after purified diphtheria toxoid injections. Included among these are: (a) arthus reactions after immunization injections with toxoid; (b) asthmatic symptoms following a routine "booster" dose of toxoid, as was observed in a patient possessing a high titer of antitoxin with the characteristic properties of the atopic reagin; (c) typical delayed tuberculin-type sensitivity to diphtherial toxin or toxoid in persons who have recovered from infections with *Corynebacterium diphtheriae.*

The antitoxic response to an injection of toxoid may take three forms: (1) Precipitating antitoxin appears in the γ-2 or slow-moving fraction of the γ-globulin, fixes complement, shows a pronounced Danysz effect, and passively sensitizes guinea pigs to anaphylaxis. (2) Antitoxic reagin is found in the γ-1 or fast-moving fraction of gamma globulin, mediates the immediate wheal type of skin reaction, and can be passively transferred to normal skin, a property

which is heat labile. This antibody does not fix complement and possesses most of the charactertistics of the atopic reagin. (3) This type of human antitoxin appears in the γ-2 globulin fraction and resembles the "blocking antibody" in treated hay fever cases. It is nonprecipitating, does not fix complement, does not fix at the site of intracutaneous injection, and has a greater affinity for toxin than the antitoxic reagin. Evidence that the antitoxic reagin is actually an antitoxin consists, in part, of the following: (a) antitoxic reagin is demonstrable only in Schick-negative persons; (b) the reagin is neutralized by the exact amount of toxoid needed to combine with the antitoxin present; (c) heating at 56° C. for four hours destroys the skin-sensitizing property of the reagin but not its toxin-binding power; (d) antitoxic reagin may be completely co-precipitated by mixing with suitable amounts of purified toxoid and γ-2 precipitating antitoxin, leaving the supernatant without its skin-sensitizing capacity.

The antitoxic reagin titers in patients who form this type of antibody tend to remain high for years, thus resembling the common atopic reagin, while the nonskin-sensitizing antitoxins in the serum tend to decline rapidly.

The type of antibody which a given individual will produce after immunization with a foreign protein cannot be predicted. However, a close correlation between immediate skin reactions to the control toxoid employed in the Schick test and a personal or familial history of allergy was noted in a group of 100 Schick-negative medical students. Following a booster dose of purified toxoid, this correlation was no longer apparent.

No circulating antibody has been demonstrated in delayed hypersensitivity to diphtheria toxin or toxoid. However, the transfer of sensitivity to tuberculin has been effected in man and animal by the use of leukocytes from sensitive donors. This type of transfer has recently been demonstrated in man even with desoxyribonuclease and ribonuclease-treated extracts of completely disrupted leukocytes.

The delayed type of sensitivity follows infection with *C. diphtheriae* and is not produced by active immunization with toxoid. In studies on adults who showed delayed inflammatory reactions (pseudoreactions) to purified toxoid used in Schick test controls, transfer of this delayed type of sensitivity was accomplished by means of leukocytes from these donors and with extracts of these white blood cells. The recipients were Schick-positive but developed the delayed type of skin reactivity to purified diphtheria toxoid. Sensitivity developed in 24 hours, became maximal 5 to 19 days after transfer, and was declining at one month. Antitoxin could not be demonstrated in the recipients' sera while they manifested this sensitivity. This was unusual in that subjects who are sensitive to diphtherial proteins almost invariably have readily demonstrable serum antitoxin titers.

It is hoped that many other problems may be solved by continued investigation employing the diphtheria toxin system.

Asthma and Hay Fever

The Use of Sonic Vibrations in the Preparation of Fungous Extracts. Kaplan, L.: Ann. Allergy **13**: 271, 1955.

Extracts of 10 species and strains of Alternaria and related genera and of isolates of Cladosporium sp. and Epicoccum sp. were prepared by subjecting suspensions of these molds to sonic vibrations of 9,000 cycles per second for 30 minutes. This treatment ruptured most cells but had little or no denaturation effect on the chemical identity of the cell material.

The extracts prepared in this manner were compared by scratch test with commercial Alternaria extracts and other inhalant allergens in a series of 75 children ranging in age from 3 to 11 years. Nineteen of the patients (25.3 per cent) reacted to one or more of the experimental mold extracts. Every patient who reacted to the commercial extract also reacted to the experimental extract, but there were 12 patients with negative reactions to the commercial extract who reacted to the experimental extracts. Although the various species of Alternaria were taxonomically identical, reactions to one extract of *Alternaria tenuis* were not necessarily accompanied by positive reactions to all of the isolates of *Alternaria tenuis*. Hence, an antigen common to all species of Alternaria probably does not exist. It would appear that more potent specific extracts of fungi may be obtained through the use of sonic energy. H. F.

C-Reactive Protein in Bronchial Asthmatic Patients. II. Further Evaluation. Aaronson, A. L., Kaplan, M. A., Goldin, M., Libretti, A., and Goldman, B.: Ann. Allergy **13**: 586, 1955.

Among 201 allergic children and 103 allergic adults, it was noted that the C-reactive protein (CRP) determinations were considerably higher in infectious than in sensitive asthmatics, with mixed cases in an intermediate position. These findings were more clear-cut in children than in adults. Patients with infectious asthma who had had recent upper respiratory infections frequently were positive for CRP. In a control group of 43 nonallergic children, there were no positive CRP reactions following upper respiratory infections. H. F.

Fungating Ioderma Treated With Hydrocortisone. Aquilina, J. T., and Bissell, G. W.: J. A. M. A. **158**: 727, 1955.

A 37-year-old man with bronchial asthma was given an expectorant containing potassium iodide. Within 24 hours, cephalalgia, ocular burning, swelling of the submaxillary glands, and a generalized pustular eruption developed. By the second day there were fungating, granulomatous, necrotic lesions extending over the forehead, malar eminences, bridge of the nose, and around the eyes. Histologic findings were consistent with those of ioderma. The patient was treated intravenously with hydrocortisone and physiologic saline. Within 3 days there was pronounced improvement. Topical hydrocortisone was then used and clearing was complete by the sixth week. The patient died 3 months later from acute glomerular nephritis. M. C.

Massive Asthmatic Atelectasis. Rakower, J., Wayl, P., and Halberstadt, H.: Dis. Chest **27**: 573, 1955.

Two cases of massive asthmatic atelectasis are reported. The first patient, an 8-year-old boy, experienced several bouts of massive asthmatic atelectasis over a period of about 2 years. All of these bouts of atelectasis were followed by complete clearing of clinical and x-ray signs within 4 to 10 days following institution of therapy, which consisted of antibiotics and antiasthmatic drugs. The second patient, a 15-year-old girl with a 12-year history of asthma, experienced massive asthmatic atelectasis involving the right upper lobe. The condition cleared within 6 days. A review of the literature on treatment of this interesting complication of asthma is included. E. W.

Dermatology

Hexachlorophene (G-11) in the Treatment of Eczematous Dermatoses. Epstein, S.: Arch. Dermat. **71**: 693, 1955.

Hexachlorophene (G-11) was used as an antiseptic in the treatment of secondary infection in patients with chronic eczematoid dermatitis. This chemical is of value as an antiseptic because it is nonstaining, inexpensive, and has a low sensitizing index. The hexachlorophene was incorporated in a concentration of 1 or 2 per cent into the following types of preparation: zinc oil, sulfonated bitumen paste, ointment base, oil-in-water emulsion base, buffered solution of aluminium acetate in a hydrophilic base, and sulfonated bitumen lotion. The most commonly used preparation was the hexachlorophene zinc oil which was employed, along with wet dressings, in all types of dermatitis. The hexachlorophene sulfonated bitumen paste was used primarily in eczema of the hands and stasis dermatitis. Hexachlorophene was often used in combination with crude coal tar to prevent folliculitis or secondary infection.

The hexachlorophene preparations were tolerated very well. In most cases where the patients complained that the preparation did not agree with them, the control preparation without hexachlorophene was also not tolerated. Only one case of definite sensitivity to hexachlorophene was encountered among hundreds of cases treated. Repeated patch tests confirmed the clinical sensitivity.

In vitro studies using the disk method on blood agar showed that hexachlorophene was bacteriostatic against *M. pyogenes, var. aureus,* hemolytic streptococci, and coagulose-positive staphylococci, but that *P. aeruginosa* was resistant to it. Clinical experience indicated that hexachlorophene was not effective in treating Pseudomonas infections. The author concludes that hexachlorophene in a 1 per cent or 2 per cent concentration has proved to be a valuable and practical antiseptic for the treatment of infectious eczematoid dermatitis. R. W.

Topical Hydrocortisone-Oxytetracycline Therapy. Stritzler, C., and Frank, L.: Arch. Dermat. **71**: 736, 1955.

The authors evaluated an ointment consisting of 1 per cent hydrocortisone and 3 per cent oxytetracycline (Terramycin) in a petrolatum base. Four hundred fifty-two patients with various dermatologic conditions were studied and, whenever possible, paired symmetrical comparisons were made. The patients studied fell into three groups. The first group included those patients with primary cutaneous infections such as impetigo, folliculitis, or sycosis vulgaris. The second group included those cases in which an underlying skin condition, such as atopic dermatitis, seborrheic dermatitis, nummular eczema, or stasis eczema was complicated by a secondary infection. The third group was essentially the same as the second group except that it included patients suffering from the basic condition without a secondary infection.

The effectiveness of the combined hydrocortisone-oxytetracycline ointment was compared to that of hydrocortisone ointment, to that of oxytetracycline ointment, and to that of the vehicle alone. In patients with primary infections, there was little difference between the results obtained with the combined ointment and with the oxytetracycline ointment. Both of these ointmens were superior to hydrocortisone ointment when used alone. In subjects with an eruption such as atopic dermatitis complicated by superimposed infection, the combined ointment appeared to be definitely superior to either ointment used separately. Fourteen of the 39 atopic dermatitis patients, who had positive Kligman tests indicating active secondary infection, showed a significantly better response to the combined ointment. All the other patients suffering from a noninfected type of dermatitis did as well on hydrocortisone ointment as on the combined ointment. No patient showed a response which suggested that the addition of hydrocortisone to the antibiotic ointment interfered with the

cutanous defense against infection. In the third group of patients in whom there was clearly no evidence of infection, the oxytetracycline gave definitely poorer results than did the hydrocortisone or the combined ointment. Since many patients in the third group with a condition such as nummular or chronic eczema but with no clinical or laboratory evidence of infection manifested a better response to the combined ointment, the authors suggest that there may be a hidden infectious component in some of these cases of dermatitis. R. W.

Comparison of Patch and Contact Test Responses in Chromate Sensitivity. Gaul, L. E.: Ann. Allergy **13**: 243, 1955.

Patch tests with various dilutions of aqueous chromate solution demonstrated that the degree of reactivity induced in sensitive individuals is directly proportional to the concentration of the testing solution employed. Although a 0.1 per cent solution appeared to be sufficiently strong for the detection of sensitivity via the patch test, a 1.0 per cent solution seemed to be perfectly safe. Stronger solutions, however, may cause undesirable reactions, such as chrome ulcers and induced sensitivity. Contact tests performed with moistened squares of filter paper and allowed to dry on the patient's back simulate actual exposure to chrome under working conditions. Stronger dilutions were required to evoke a positive contact reaction than were needed to induce a positive patch reaction. The direct application of a drop of chromate solution to the skin gave reactions of the same intensity as those induced by the contact tests. Among a series of 243 patients, there were 34 who gave positive patch reactions to the 1.0 per cent solution. Positive patch reactions varied in intensity from a simple erythema to vesiculation and/or pustules. In none of the patients tested was there any lighting up of previous sites of chrome dermatitis. Although chrome dermatitis may occur in patients not actually working with the material, the majority of such cases occur in individuals employed in the chromium industry and among printers, cement workers, or workers using chrome-tanned leather gloves. H. F.

Failure to Transfer Allergic Eczematous Hypersensitivity From Man to Guinea Pig. Rosenthal, S. A., Litt, J. Z., and Baer, R. L.: J. Invest. Dermat. **24**: 483, 1955.

Viable white blood cells obtained from the blood of 5 human subjects suffering from eczematous contact type sensitivity were injected intraperitoneally into 5 guinea pigs. After 24 hours, an epilated area on the flank of each recipient animal was tested by inunction of a small drop of the material to which the human subject was known to be strongly sensitive. The test substances were resorcin, paraphenylenediamine, nickel sulfate, and turpentine. The test sites were read after 24 and 48 hours. Similar inunction tests at other freshly prepared sites were repeated on the second day after injection of the cells and on later days. In no instance did a positive patch test reaction occur. It was concluded that allergic eczematous contact type sensitivity was not transferable by this method. M. C.

Contact Dermatitis From Chlorpromazine. Lewis, G. M., and Sawicky, H. H.: J. A. M. A. **157**: 909, 1955.

Two nurses with chronic contact dermatis of the eyelids, face, and hands of undetermined etiology were found to be handling chlorpromazine (Thorazine) in their work. Patch tests were made with this drug in a concentration of 25 mg. per milliliter. In the first case the patch was left on for 10 hours, and in the second case for 2 hours. In each instance, a markedly positive patch test

reaction resulted which was associated with an acute flare-up of the dermatitis. The exacerbations of the lesions were so severe that from one to two months of intensive therapy was required before the nurses could return to work.

An attempt was made to sensitize 50 men by the application of a 25 per cent solution of Thorazine at 3-day intervals for a total of three applications. Challenging patch tests were done one month later, and all these tests gave negative reactions. In no case was there evidence of primary irritation of the skin. It was concluded that chlorpromazine is not a strong sensitizer and that sensitization to it can be prevented by the avoidance of frequent and prolonged contact with the drug. M. C.

Otorhinology and Ophthalmology

Ocular Allergies. Donegan, J. M.: Ann. Allergy **13**: 559, 1955.

Because of its fine texture, the skin of the eyelids is highly susceptible to inflammatory and allergic reactions. Contact allergy to cosmetics and drugs is the most common form of acute dermatitis of the lids. When due to cosmetics, the reaction often begins at the medial portion of the upper lid; when due to locally instilled drugs, it usually begins as a conjunctivitis. Contact allergies due to cosmetics are most often caused by impurities in these preparations or by perfumes. Synthetic resins, lanolin, cocoa butter, almond oil, indelible lipstick dyes, and certain chemicals in hair dyes and rinses are the most common of the cosmetic allergens. Orris root and rice powder are, at the present time, rarely used in the manufacture of cosmetics and are no longer important allergens. Allergic reactions to ophthalmic drugs must be differentiated from irritative reactions caused by products of deterioration which may form in such medications on ageing. Eczema of the eyelids may result from the systemic use of such drugs as bromides, phenolphthalein, antipyretics, iodides, and barbiturates. In addition to allergic reactions, infectious eczematoid staphylococcal dermatitis of the eyelids is probably the most common form of dermatitis from contact allergy.

The conjunctiva may be the seat of allergic reactions, such as vernal catarrh and phlyctenular conjunctivitis. Interstitial keratitis, a condition usually found in patients with congenital syphilis, is believed to be due to an allergic reaction to the toxins of the spirochete. The cornea may be the seat of punctate ulcers due to allergic reactions to foods or contactants.

The steroids used locally in the eye may be of great benefit, but caution must be exercised in their use since viral diseases of the eye and dendritic keratitis may be aggravated by them and result in perforating ulceration. Keratoconus may also be an allergic manifestation. The sclera, uveal tract, optic nerve, and retina may be the sites of allergic reactions to tuberculoprotein. Recent findings, however, seem to indicate that about 25 per cent of uveal irritations of undetermined origin are due to toxoplasmosis rather than to allergy. H. F.

Miscellaneous Allergies

The Penicillin Content of Poliomyelitis Vaccine (Salk) and Its Administration to Allergic Patients. Siegel, S.: Am. J. Pub. Health **45**: 791, 1955.

In a series of experiments, it was demonstrated that the penicillin content of the Salk poliomyelitis vaccine is not great enough to make it a hazard as a potential sensitizer or anaphylactogen. Sixteen allergic individuals known to

be skin sensitive to pollen, inhalants, and foods comprised the test group. All gave strongly positive reactions to extracts of animal danders and 3 gave positive reactions to extracts of beef, pork, and lamb. Eleven of the group were clinically sensitive to animal danders. Intracutaneous tests with the polio vaccine yielded negative or plus-minus reactions in 14 of the subjects and 1-plus reactions in 2. Eleven of the group, including the 2 patients who showed the positive skin reactions, were given 1.0 ml. of the undiluted vaccine subcutaneously with no evidence of any local or constitutional reaction. Sixty-three control subjects tested intracutaneously with the vaccine gave negative or plus-minus immediate reactions. Of 58 subjects tested for delayed responses, 3 showed slight reactions at 24 hours which had practically disappeared at 48 hours. Intracutaneous tests for delayed reactions to the vaccine performed on a known penicillin-sensitive subject gave negative results in contrast to a strongly positive reaction obtained on this subject with a 10 unit per milliliter dilution of penicillin. The subcutaneous injection of 1.0 ml. of the vaccine failed to induce either a local or systemic reaction in this patient. The vaccine also failed to elicit positive reactions in passive transfer sites prepared with the serum of an anaphylactically penicillin-sensitive patient, whereas penicillin in a dilution of 0.5 unit per milliliter produced positive reactions in these sites.

These findngs indicate that the Salk vaccine probably contains less than 0.5 unit of penicillin per milliliter. They further indicate that the presence of positive skin reactions and clinical sensitivity to animal danders and proteins is no contraindication to the administration of Salk vaccine. H. F.

Studies on a Skin Test for Western Equine Encephalitis. Preliminary Evaluation In Man. Shinefield, H. R., Longshore, W. A., Jr., and Lennette, E. H.: J. Immunol. **75**: 227, 1955.

Skin testing was performed with a formalinized preparation of Western equine encephalitis virus-infected allantoic and amniotic fluids from hens' eggs. Control material consisted of the same fluids from uninoculated eggs. Various dilutions of the skin test antigen and control material were injected intracutaneously in 0.1 ml. amounts into the midflexor surface of the arms of 172 control subjects and 44 immune individuals. These 44 subjects had had this type of encephalitis one year prior to skin testing and had shown serologic evidence of the disease at the time of testing. From these studies, the skin test for Western equine encephalitis appeared to be specific when a 1:10 dilution of skin test antigen was employed and the reaction was read at 48 hours. The reaction was considered to be positive if the palpable induration measured more than 5 mm. or the erythema measured 15 mm. or more. On the basis of these criteria, 52 per cent of the children and 84 per cent of the adults of the immune group showed positive reactions. There was no correlation between the degree of dermal reactivity and the level of complement-fixing or neutralizing antibody titers in this group. Skin testing with a 1:10 dilution of antigen failed to produce detectable complement-fixing or neutralizing antibodies in the control susceptible subjects. However, skin testing the immune group with this dilution of antigen appeared to serve as a mild recall stimulus for antibodies, particularly in the adults. The authors emphasize that the criteria for a positive dermal reaction are tentative and may have to be changed when additional information is accumulated. B. S.

The Application of the Middlebrook-Dubos Hemagglutination Test in Tuberculosis of Children. Choremis, C. B., and Anastasea, K. N.: Am. Rev. Tuberc. **70**: 139, 1954.

The Middlebrook-Dubos hemagglutination test was investigated in 340 patients treated at a pediatric clinic in Athens, Greece. There were 229 patients with tuberculosis and 111 control subjects. Of the 229 tuberculous patients, there were 25 with positive tuberculin reactions but without clinical symptoms, 42 who had been vaccinated with BCG, and 162 with tuberculosis of various types. These included 6 with miliary tuberculosis, 90 with tuberculous meningitis, 5 with tuberculosis of the mediastinal lymph nodes, 15 with pleurisy, 2 with osteoarthritis, 2 with erythema nodosum, 30 with primary complex, and 12 with subsiding adenitis. In the 111 nontuberculous patients, the serum hemagglutination reaction was negative except in two patients in whom it was weakly positive. Of 25 patients with positive tuberculin reactions, but with no other evidence of the disease, the hemagglutination reaction was weakly positive in 15. Of 42 BCG-vaccinated persons, the hemagglutination reaction was positive in 31 and negative in 11. In 162 tuberculous patients, the hemagglutination reaction was positive in 98 per cent and negative in 2 per cent. The average value of the hemagglutination titer was related to the severity of the tuberculous infection. The highest hemagglutination titer, an average value of 19.33, was found in miliary tuberculosis. An average value of 16.26 was found in tuberculous meningitis, with lesser values present in mediastinal lymphadenitis, pleurisy, primary complex, and following BCG vaccination. The titer was low during recovery from all types of infection, as judged by clinical or laboratory criteria, and was also low during periods shortly before death. A rough parallel was found to exist between the hemagglutination reaction and the tuberculin reaction. The tuberculin reaction, high at the beginning of the disease, increased with the improvement of the patient's condition, and remained high until recovery. On the contrary, the hemagglutination reaction, rather low at the beginning of the disease, increased gradually until it reached a peak in the middle of the disease and then gradually decreased and sometimes disappeared completely when recovery occurred. E. W.

Anaphylaxis

Lipemia Clearing in Peptone and Anaphylactic Shock. Worley, L. M., and Lequire, V. S.: Proc. Soc. Exper. Biol. & Med. **89**: 181, 1955.

Peptone or anaphylactic shock was induced in dogs by intravenous injection of the excitant. Four to six hours prior to testing, lipemia was produced by feeding a fatty meal. Blood samples were drawn before and 5 minutes after shocking. From those animals which survived, 10- and 30-minute blood specimens were also obtained. Six of the 7 dogs injected with peptone developed shock and demonstrated a prolonged blood-clotting time. Two of 3 egg albumin-sensitized dogs were successfully shocked with the antigen and they demonstrated a prolonged clotting time. In vitro lipemia clearing occurred in samples from each of the 8 shocked animals. In vivo lipemia clearing was noted in only 2 of the 8 shocked animals. The 2 animals which were not shocked demonstrated normal blood-clotting times and failed to show evidence of either in vitro or in vivo lipemia clearing. Protamine sulfate was injected into 2 animals at the height of shock and in both animals in vitro lipemia clearing failed to occur, suggesting that heparin or a heparin-like substance was responsible for clearing factor formation. The discrepancy between in vitro and in vivo lipemia clearing in the shocked animals can be explained by the presence of hypoxia usually present in anaphylactic shock. It has been found that hypoxia inhibits the in vivo activity of the lipemia clearing factor but does not inhibit its formation. Therefore, in shock, the in vitro activity of this factor remains unaffected. B. S.

Anaphylaxis and Histamine Shock in Mice. Parfentjev, I. A.: Proc. Soc. Exper. Biol. & Med. **89**: 297, 1955.

Young female mice, weighing about 20 grams, of strains CFW and hybrids C-58F-1 and Princeton, were sensitized with H. pertussis vaccine. The vaccinated mice of CFW developed a high sensitivity to histamine and showed 100 per cent mortality. Only a small percentage of unvaccinated mice of the same age and strain succumbed from similar doses of histamine. The animals of the other two strains failed to show sensitivity to histamine, even when the sensitizing dose of H. pertussis vaccine was doubled. Vaccinated mice of all three strains developed sensitivity to H. pertussis nucleoprotein and a high mortality resulted from anaphylactic shock. It appears, therefore, that the genetic factor is important in histamine sensitivity of H. pertussis-vaccinated mice. B. S.

Soybean: Anaphylactogenic Properties. Ratner, B., and Crawford, L. V.: Ann Allergy **13**: 289, 1955.

Soybean extract injected intraperitoneally in single or multiple doses and soybean flour administered by inhalation proved to be poor anaphylactogens in guinea pigs. It was further demonstrated that guinea pigs that had never ingested soybean and that had been bred from mothers on a soybean-free diet reacted in the same manner as those fed on soybean. There was some evidence of a slight increase in the anaphylactogenic property of soybean when Freund's adjuvant was combined with the soybean extract used for sensitizing the experimental animals. H. F.

Pharmacology, Physiology, and Pathology

Relative Effects of Various Agents on Complement and Antibody Production. I. Rice, C. E.: J. Immunol. **73**: 375, 1954.

Groups of guinea pigs were injected subcutaneously with one of three complement-depressing agents, namely, carbon tetrachloride, ethionine, and gum acacia. Rabbits were treated with either ethionine or gum acacia. Carbon tetrachloride and ethionine act by inducing fatty infiltration of the liver and serum protein changes. Gum acacia accumulates in the reticuloendothelial system and in the parenchymal cells of the liver and also affects serum protein synthesis. After two weeks of treatment with one of these agents, the animals were sensitized intraperitoneally with *Brucella abortus* vaccine. Blood taken before and during immunization was titrated for hemolytic complement and agglutinative and complement-fixing activity with *Br. abortus* antigens. Treated nonimmunized and untreated immunized animals in each group served as controls. Other groups of rabbits and guinea pigs were fed diets, sufficiently high in cholesterol to produce fatty infiltration of the liver. After about two weeks on this diet, half of the animals were immunized. Bloods of the immunized and nonimmunized animals on the high-cholesterol diet were studied in the manner described above.

Treatment of guinea pigs with ethionine or carbon tetrachloride caused a decline in complement titer, but did not significantly affect the development of agglutinating or complement-fixing antibodies against *Br. abortus*. Ethionine-treated rabbits reacted similarly. Guinea pigs and rabbits receiving gum acacia showed a reduction in complement as well as a reduction in agglutinating and complement-fixing antibody titers. The animals fed on the high-cholesterol diet failed to show any deviation from normal in complement, antibody, and total serum protein production.

These studies indicate that one agent may have a similar or different effect on complement and antibody production in the same animal. The possibility should be considered in evaluating the effect of any particular factor upon a state of immunity believed to be dependent upon the combined action of complement and antibody. B. S.

Control of Pulmonary Edema With Silicone Aerosols. Nickerson, M., and Curry, C. F.: J. Pharmacol. & Exper. Therap. **114**: 138, 1955.

This study was prompted by the death of a mitral stenosis patient from acute pulmonary edema. In a 2-hour period she had expelled 3 liters of froth which, on standing, settled down to 200 ml. of fluid. Foam seems to be an important barrier to the passage of tidal air to and from the alveoli. Aerosolized silicone emulsions were found to be effective in protecting rabbits and rats against pulmonary edema induced by intravenous epinephrine or by the inhalation of chlorine gas. A favorable effect was noted in from 2 to 3 minutes. Emulsions of 30 per cent by weight of various silicone products plus 10 per cent of polyoxyethylene stearate and 4 per cent of glyceryl monostearate, identified as XEC 151, XEF 215, and XEF 216, were most effective. Foaming of a 10 per cent serum solution can be prevented by the addition of as little as 0.02 μg per milliliter of the emulsion of XEC 151. Post-mortem examinations of animals that died or were sacrificed following silicone treatment of experimental pulmonary edema showed some fluid in the alveoli but no foam in the trachea or bronchi. In the control animals, on the other hand, there was a great deal of foam. Lung weights of treated and untreated animals were the same. Although aerosols did not prevent the accumulation of fluid, they afforded significant protection against death from pulmonary edema. Normal dogs exposed to XEC 151 aerosol for 15 minutes had no alteration of alveolar oxygen exchange or arterial oxygen saturation. Rats treated daily for up to 28 days showed no inflammatory or granulomatous changes in the lungs, despite the presence of silicon dioxide. Slight interstitial edema, a few small areas of atelectasis, and minimal mononuclear cell infiltration were found in both treated and control animals. Rabbit eyes were irritated by the silicone solution. Toxicity studies of the dimethylpolysiloxanes indicate that these compounds have little or no systemic or local toxic effects. Silicone emulsion aerosols are recommended for clinical trial in pulmonary edema in man. E. K.

The Effect of Hydrocortisone on the Oxygen Uptake of Inflamed Tissue. Heim, H. C., Deitrich, R. A., and McDonald, J. G.: J. Pharmacol. & Exper. Therap. **114**: 51, 1955.

Subcutaneously injected croton oil produced a granulomatous inflammation in an air sac in rats. Hydrocortisone was injected into the granuloma pouch 2 days later. After 48 hours the animals were sacrificed and the oxygen uptake of the homogenized granulomatous tissue was compared in the hydrocortisone-treated animals and in the controls. Potassium adenylate was added to some of the tissue culture flasks. Readings were also taken of uninflamed areolar tissue one hour after the subcutaneous injection of air. The Q_{O_2} (quantity of oxygen used per milligram of dry tissue per hour) of normal areolar connective tissue was approximately 0.1; that for croton-inflamed tissue was 2.56 where adenylate was added and 1.49 in tissue cultures without adenylate. Hydrocortisone-treated inflammatory tissue had a Q_{O_2} of 5.68 with adenylate and 2.99 without adenylate. Substitution of desoxycorticosterone acetate, progesterone, or cholesterol for hydrocortisone did not increase tissue respiration. Hydrocortisone was ineffective if added in vitro. It was concluded that both hydrocor-

tisone and adenylate increase the Q_{O_2} of inflamed tissue and that hydrocortisone administered in vivo augments the increase in Q_{O_2} produced by adenylate in the tissue cultures. E. K.

The Enzymatic Demethylation of Ephedrine. Axelrod, J.: J. Pharmacol. & Exper. Therap. **114**: 430, 1955.

Rabbit livers and other organs were homogenized and centrifuged differentially to remove unbroken cells, nuclei, mitochondria, and microsomes. Ephedrine was incubated with these fractions. The degree of enzymatic demethylation of this drug was determined by estimating the amount of formaldehyde formed. Norephedrine formation was also quantitatively measured. Liver demethylated ephedrine to norephedrine and formaldehyde, but lung, diaphragm muscle, kidney, and brain tissues were inactive. The reaction required triphosphopyridine nucleotide (TPN) and oxygen, took place mainly in the microsomes of the liver, and was most effective in the presence of "soluble fraction."

The TPN dehydrogenases in the soluble fraction maintain a reservoir of reduced TPN which is important to the breakdown of ephedrine. There is also evidence that ephedrine is metabolized by mechanisms other than demethylation. The activity of ephedrine demethylating enzyme and the presence of a heat-labile inhibitory factor in microsomes vary with different species. A heat-stable factor which stimulates ephedrine demethylation was also found in microsomes. Of several species tested, rabbit liver was most active in demethylation of ephedrine, with dog, guinea pig, and rat livers following in that order. E. K.

Studies on Prophenpyridamine (Trimeton) and Chlorprophenpyridamine (Chlor-Trimeton). Labelle, A., and Tislow, R.: J. Pharmacol. & Exper. Therap. **113**: 72, 1955.

Some 70 compounds were screened for antihistaminic activity. Particular attention was paid to Trimeton and Chlor-Trimeton. The therapeutic index for Chlor-Trimeton orally in guinea pigs was calculated by the conventional formula as 1550, as compared with 170 for Trimeton, 70 for Benadryl, and 60 for Pyribenzamine. Chlor-Trimeton, on a weight comparison basis, was found to be the most effective of the compounds tested in protecting guinea pigs against horse serum anaphylaxis. Chlor-Trimeton had a local anesthetic activity equal to procaine but less than that for Benadryl or Pyribenzamine. Buffering of the solution to pH 7.4 was important in increasing the local anesthetic potency of all the antihistamines. Chlor-Trimeton applied in 0.25 per cent concentration to rabbit eyes daily for 30 days failed to cause irritation. A 10 per cent solution was tolerated subcutaneously by guinea pigs.

Chlor-Trimeton and Pyribenzamine did not inhibit the depressor effect of intravenously administered arecoline. Benadryl and atropine abolished the depressor effect of this drug entirely. Intestinal spasm induced by carbamylcholine was counteracted by atropine 0.006 mg. per liter, Benadryl 1.0 mg. per liter, Chlor-Trimeton 5.0 mg. per liter, and Trimeton 6.7 mg. per liter. These antihistamines were equal in ability to relax spasm induced by barium chloride. E. K.

Influence of Hormones (Growth, ACTH, Thyrotrophic and Cortisone) Upon Complement Level in Rabbits. Gordon, P., and Benditt, E. P.: Proc. Soc. Exper. Biol. & Med. **89**: 286, 1955.

Rabbits were immunized intravenously for 3 weeks with small amounts of a solution of bovine serum albumin and bovine gamma globulin. Serum complement levels showed a slight rise during this period. When part of this group was treated simultaneously with cortisone, a marked and persistent depression in serum complement was noted. In one cortisone-treated group, growth hormone was also administered during the second and third weeks, and the serum complement levels rose toward normal. Growth hormone administered alone, one week after the onset of immunization, caused a marked rise in complement levels. ACTH failed to affect the serum complement in immunized animals.

These hormones were then administered in the same manner and dosage to nonimmunized rabbits. Untreated animals showed a slight rise in complement. Cortisone failed to produce the significant fall in titer that it produced in the immunized group. ACTH was without effect in both normal and immunized animals. Growth hormone produced the same marked rise in complement. Thyrotrophic hormone, a known contaminant of the growth hormone preparation used, caused a similar but less marked increase in serum complement.

Cortisone and growth hormone have opposing effects on complement in the rabbit. The evidence suggests that the growth hormone effect is produced by the contaminating thyrotrophic hormone. The authors believe that the cortisone effect on complement was not noted by other workers because their doses of antigen were too large. B. S.

Radioactive Iodine in the Management of Patients With Severe Pulmonary Emphysema. Hurst, A., Levine, M. H., and Rich, D. R.: Ann. Allergy **13**: 393, 1955.

The radioactive effect of I^{131} on the thyroid has benefited patients with angina pectoris and chronic congestive heart failure by lowering the basal metabolic oxygen needs and thus making available a relatively larger amount of tissue oxygen for other purposes. With this in mind, a series of 28 patients, ranging in age from 44 to 71 years and suffering from severe emphysema, were treated with I^{131} after appropriate preliminary studies. In a follow-up of 24 of the 28 cases, it was found that 2 had experienced marked relief, 8 had a good result, and 9 had a fair result. The remaining 5 patients had died of congestive heart failure early in the course of treatment. In addition to radioactive iodine treatment, it is necessary to continue these patients on other established methods of therapy. H. F.

Periarteritis Nodosa: Recognition and Clinical Symptoms. Blankenhorn, M. A., and Knowles, H. C., Jr.: Ann. Int. Med. **41**: 887, 1954.

From analysis of autopsy and biopsy material, 45 cases of necrotizing angiitis (fibrinoid necrosis and inflammatory reaction in vessel walls) were divided pathologically into 2 groups—classic periarteritis nodosa and hypersensitivity angiitis.

There were 35 cases of periarteritis nodosa which clinically could be subdivided into 21 cases of so-called secondary and 14 cases of primary periarteritis nodosa. Those cases designated as secondary periarteritis nodosa were found to be an end stage of hypertensive renal disease in which lesions of periarteritis nodosa had developed shortly before death. Pathologically, they showed periarteritis nodosa of short duration, but clinically they were examples of severe renal disease with hypertension. The clinical findings of periarteritis nodosa were masked by those of renal disease and hypertension. It was felt that hypertensive renal disease was probably an etiological factor in some cases of periarteritis nodosa. The cases of primary periarteritis nodosa showed widespread

lesions in various stages. Clinically, they were characterized by a long course with gastrointestinal symptoms, peripheral neuropathy, hypertension, and occasionally eosinophilia.

There were 10 cases of hypersensitivity angiitis. These were manifested clinically by a fulminating course with fever, skin rash, nephritis, myocarditis, and often a history suggesting recent exposure to an antigenic substance.

It is suggested that periarteritis nodosa and hypersensitivity angiitis represent two distinct disease entities and that they can be differentiated clinically as well as pathologically. The pathologic changes in both conditions were compared. J. S.

Passive Cellular Transfer of Hypersensitivity to Serum Antigens in Rabbits. Tremaine, M. M., and Jeter, W. S.: J. Immunol. **74**: 96, 1955.

The authors report the successful passive transfer of cutaneous reactivity to serum antigens by the use of peritoneal exudative leukocytes from rabbits sensitized to the point of typical Arthus reaction. Normal horse serum, beef serum, and crystalline bovine serum albumin were the antigens employed.

Animals were sensitized by daily intracutaneous injections of 0.1 ml. of antigen until a typical hemorrhagic Arthus reaction developed. Several days later, sterile mineral oil was given intra-abdominally to provoke a peritoneal exudate. After 48 hours, the abdominal cavity was washed out with modified Locke's solution containing gelatin and heparin. The cells were sedimented by centrifugation, washed in Locke's solution, and resuspended in fresh solution for injection into recipient animals by various routes. Antibody levels were determined in the recipients before and after injections of the cell suspensions. Intracutaneous tests with the antigen were made at intervals on the recipients to detect the presence of cutaneous sensitivity. Positive reactions were read on the basis of erythema, edema, and induration.

Cutaneous sensitivity developed in the recipients of cells from Arthus-sensitized donors. The positive reaction appeared about 5 hours after the intracutaneous test was made. The reaction reached its maximum in 18 to 24 hours and persisted from 3 to 4 days. Edema and induration were constant features, but hemorrhage and necrosis were never observed. Similar results were obtained when the donors' cells were injected intravenously, intraperitoneally, subcutaneously, or intracutaneously in the recipient, indicating that total body, rather than local, sensitization occurred. Cells from nonsensitive animals failed to produce any sensitivity. Triplicate washing of the donors' cells did not materially affect the results. Attempts to extract precipitins from the donors' cells by three different extraction methods were unsuccessful. The precipitin titers in the recipients' sera after transfer were not increased, nor were their sera able to passively sensitize guinea pigs. Hence, it did not seem likely that the donors' circulating antibodies could be responsible for the positive transfer.

Following the transfer of cells from Arthus-sensitive donors, cutaneous sensitivity appeared 5 to 8 hours later and reached a maximum at 2 to 5 days. Sensitivity lasted from 2 to 11 days. At this time, many of the animals developed active sensitization as a result of the serial testing with the antigen. Crystalline bovine serum albumin and whole beef serum produced positive but less striking results with cellular transfer than those observed when horse serum was employed as the antigen. B. S.

Miscellaneous

Tropical Eosinophilia Treated With ACTH. Sanjivi, K. S., Thiruvengadam, K. V., and Friedmann, H. C.: Dis. Chest **28**: 76, 1955.

Tropical eosinophilia, a disease manifested by low-grade pyrexia, coughing, wheezing, anorexia, loss of weight, eosinophilia, and mottling of the lungs, is regarded by the authors as an allergic state. Twenty-four patients, ranging in age from 12 to 36 years and manifesting the usual signs and symptoms of tropical eosinophilia, were treated with ACTH. The hormone was administered intravenously in an infusion in doses which ranged from 5 to 20 I.U. per day for 10 days. Twenty-two of the 24 patients in this series had satisfactory remissions of the disease. Most of the patients were free of symptoms on the third day. During treatment with this hormone, the absolute eosinophile count per cubic centimeter of blood, which had ranged from 3 to 50,800, dropped to minimum values between 0 and 400 per cubic centimeter in the majority of cases. Following the cessation of ACTH therapy, there was a gradual rise to about one-half the initial count in most cases. The average value for 17-ketosteroid output per day before commencement of ACTH therapy was 4.70 mg. In mid-treatment, it rose to 8.00 mg.; immediately posttreatment, the value fell to 5.47 mg. Other laboratory tests indicated a gradual fall in the erythrocyte sedimentation rate and a slight increase in the fasting blood sugar during active treatment. X-rays taken during therapy indicated marked clearing of the infiltrations. Moreover there was an increase in the average vital capacity from 1,199 c.c. prior to treatment to 1,443 c.c. after treatment. Side effects included headaches, giddiness, and substernal pain. All of these symptoms, however, were transient. In 2 patients, treatment with ACTH had to be discontinued because of the development of albuminuria. One of these patients had a transient hypertension. ACTH seemed to have a definite, though limited, place in the treatment of tropical eosinophilia. E. W.

Tropical Eosinophilia Treated With Cortisone. Sanjivi, K. S., Thiruvengadam, K. V., and Friedmann, H. C.: Dis. Chest **28**: 88, 1955.

Twenty-one patients with tropical eosinophilia were treated with cortisone in doses of 50 to 100 mg. per day for a 10-day period. Of the 21 patients, 19 showed satisfactory remission of symptoms and signs as the result of treatment. Most of the patients became symptom free between the third and fifth day of treatment. The duration of clinical remission induced by cortisone was not long-standing and was similar to the remissions induced by ACTH. Seven patients experienced side effects consisting of vague chest pains. During treatment with cortisone, there was little change in the urinary 17-ketosteroids, but there was a slight posttreatment rise in ketosteroid excretion. Treatment with cortisone induced a significant fall in the erythrocyte sedimentation rate, but the absolute eosinophile count did not fall so drastically or so dramatically as had been observed with ACTH. Although there was considerable improvement in the roentgenograms of the chest, the clearing was not so complete as that noted in patients treated with ACTH. E. W.

The Significance of a Positive L.E. Phenomenon. Weiss, R. S., and Swift, S.: Arch. Dermat. **72**: 103, 1955.

Bloods from 350 patients suffering from various medical conditions were studied for the presence of L.E. cells. The modified Zimmer-Hargraves technique was used for conducting most of the tests. Typical L.E. cells were found only when lupus erythematosus was the most likely or very probable diagnosis.

Of 46 rheumatoid arthritic patients who were studied, 5 showed typical L.E. cells and 3 had tart cells. None of the bloods from 24 patients with penicillin reactions showed the presence of L.E. cells. Only 2 of 55 patients with discoid lupus had positive L.E. smears. Five cases of pemphigus gave negative

reactions. No L.E. cells were found in patients suffering from scleroderma, periarteritis nodosa, dermatomyositis, or sensitivity to sunlight. Patients with drug reactions to tetracycline, sulfadiazine, sulfisoxazole (Gantrisin), barbiturates, bismuth, acetylsalicylic acid, bromides, chloroquine (Aralen), isoniazid (INH), pyrazinamide (Aldinamide), and chlorpromazine (Thorazine) showed no positive results. One jaundiced patient with a reaction to Thorazine showed one advanced tart cell. Of 3 patients with rheumatic fever, 1 had a positive smear. Patients with herpes zoster, severe dermatitis venenata, lymphoma, dermatitis herpetiformis, seborrheic dermatitis, and hemolytic anemia gave negative results. No L.E. cells were found in the bloods of 4 severely allergic patients.

Although difficult, it was usually possible to separate the true L.E. cell from the pre-L.E. cell (tart cell). The finding of only tart cells has led occasionally to an incorrect, premature diagnosis of lupus erythematosus. Follow-up of patients whose blood contained tart cells, however, has shown that eventually many of these individuals do develop typical lupus erythematosus.

The authors emphasize the point that the L.E. test is specific and that it should be used much more extensively, especially in cases of arthritis or undiagnosed illnessess which are suggestive of lupus. If tart cells are found, it is advised that a much more diligent search be made for typical L.E. cells. R. W.

Penicillin V: Further Observations. Martin, W. J., Nichols, D. R., and Heilman, F. R.: Proc. Staff Meet., Mayo Clin. **30**: 521, 1955.

The serum concentration of penicillin V was determined in 7 cases after the ingestion of 1,000,000 units of the antibiotic with and without coincident administration of probenecid (Benemid). The concentration of antibiotic varied between 1.2 units and 7.9 units per milliliter without probenecid and between 3.72 units and 8.65 units per milliliter with probenecid.

The diffusion of penicillin V into various body fluids and tissues was investigated. Massive oral doses of penicillin V were given to 9 patients without inflamed meninges, and in no instance was penicillin found in the cerebrospinal fluid. However, penicillin V was found to diffuse into ascitic fluid and into pleural fluid. In patients with normal hepatic function, penicillin V was concentrated in the liver and excreted in the bile in a biologically active form.

M. C.

Influence of Repeated Histoplasmin Skin Tests on Precipitins and Complement-Fixing Antibodies. Salvin, S. B., Weber, R. W., Lackman, D. B., Nishio, J., and Menges, G.: J. Lab. & Clin. Med. **44**: 56, 1954.

Thirty-two medical students were skin tested five times intracutaneously with 0.1 ml. of histoplasmin 1:100, over a period of eight weeks. Blood was taken from these volunteers prior to the initial testing and several times during the period of this study. The sera of these patients were tested by two complement fixation techniques and by one precipitation technique. Precipitation tests were carried out with broth filtrate from the mycelian phase cultures as antigen. The complement fixation tests were carried out by both 100 per cent and 50 per cent end point techniques. In the former technique, a Bengtson-type test was used with that amount of antigen which gave the highest complement fixation titer with a serum of known capacity. In the second technique, the test of Kent and Rein, as performed by Saslaw and Campbell, was used (AMS type). Three antigens were employed in the complement fixation tests: (1) Whole cells of the yeast phase, grown in broth for five days, were killed by exposure to 56° C. for one hour, washed, and resuspended in saline solution. (2) Whole cells, grown in the previously mentioned broth, killed by exposure

to 1:10,000 Merthiolate for five days at 37° C. The organisms were then ground, the mixture was centrifuged, and the clear supernate was used as antigen. (3) The broth filtrate from mycelian growth was prepared by growing the mycelium on the surface of an asparagine-glucose broth, as described by Smith. Fourteen of the 32 medical students showed no skin reactivity at any time during the course of these experiments. Practically none of the 14 skin-negative individuals showed antibodies against any of the antigens in the serologic tests employed in this study. Eighteen of the 32 medical students were skin-test positive to histoplasmin on initial testing. These reactions varied from weakly positive to strongly positive, as measured by induration diameters. After five skin tests within an eight-week period, none of the individuals showed any significant change in the diameter of the indurated area. Several subjects had brief fluctuations in the degree of skin reactivity. None of the skin-test-positive patients showed precipitins in the sera from the first bleeding. Subsequently, during the course of these experiments, 2 showed doubtful positive reactions by this method of testing, although the precipitates did not approach in size or opacity those seen with sera in proved or probable active cases of histoplasmosis. Fixation of complement was essentially negative in sera from the first bleeding. Results in the complement fixation tests with sera from subsequent bleedings depended upon the nature of the antigen and on the type of test. Histoplasmin and the soluble supernate from ground cells of the yeast-phase fixed complement with some sera from skin-test-positive individuals after they had received repeated skin tests. The demonstration of antibodies by the two soluble antigens occurred in both types of complement fixation tests, although the titers were much higher in the AMS-type test. In this test, sera from 9 of the 18 skin-positive students showed antibodies on at least one bleeding date in the presence of the soluble supernate from the ground cells of the yeast phase as antigen, sera from 9 showed antibodies with histoplasmin as antigen, and sera from 6 showed antibodies with whole yeast cells as antigen. The antibodies were of a lower titer and of shorter duration with the whole yeast as antigen than with either the soluble supernate or histoplasmin. Hence, of sera drawn after the students had been skin tested at least once, 51 per cent were positive with the soluble supernate from ground yeast cells as antigen, 67 per cent were positive with histoplasmin as antigen, and only 29 per cent with whole yeast as antigen. In the Bengtson-type test, with histoplasmin as antigen, 10 individuals who had been skin tested repeatedly had at least one positive serum; with the soluble antigen from ground cells of the yeast phase as antigen, 5 individuals had positive sera. These titers were generally lower and less frequent than those seen in the more sensitive AMS-type test. In the Bengtson-type test, using whole cells of the yeast phase as antigen, not one of the 18 sera from the skin-positive individuals who had been repeatedly skin tested developed complement fixing antibodies. E. W.

Announcement

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